



# Hypoxemia and autonomic nervous dysfunction in patients with chronic obstructive pulmonary disease

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## KEYWORDS

Heart rate variability;  
Chronic obstructive pulmonary disease;  
Autonomic nervous activity;  
Oxygenation;  
Airway narrowing

## Summary

**Objective:** Hypoxemia is known to be associated with abnormal heart rate variability (HRV) that can reflect the severity of the illness and may have prognostic value in patients with chronic obstructive pulmonary disease (COPD). The aim of this study was to examine the relationship between the derangements in cardiac autonomic nervous function and the oxygenation status or degree of airflow obstruction in COPD patients by using HRV analysis.

**Methods:** Thirty clinically stable COPD patients and 18 age-matched normal subjects were included in this study. The normalized high-frequency power (nHFP) and the low-/high-frequency power ratio (LFP/HFP) were used as indices of vagal activity and sympathovagal balance, respectively.

**Results:** Although global HRV measures were all significantly decreased, the nHFP and LFP/HFP of COPD patients were not significantly different from those of normal controls. There was a negative correlation between nHFP and arterial partial pressure of O<sub>2</sub> (PaO<sub>2</sub>) and a positive correlation between LFP/HFP and PaO<sub>2</sub> in COPD patients. No correlation existed between forced expiratory volume in 1.0s/forced vital capacity (FEV<sub>1</sub>/FVC), % predicted of FEV<sub>1</sub> (%FEV<sub>1</sub>) and nHFP or LFP/HFP in COPD patients.

**Conclusions:** The resting autonomic nervous function of COPD patients is not different from that of normal controls. Though the degree of airway narrowing is not

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related to the cardiac autonomic nervous function, chronic hypoxemia can lead to enhanced cardiac vagal activity and depressed sympathetic activity in COPD patients. A worse oxygenation status is associated with increased cardiac vagal and decreased cardiac sympathetic activities in COPD patients.  
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## Introduction

The autonomic innervations of human airway have parasympathetic cholinergic, sympathetic adrenergic and peptidergic efferent components.<sup>1,2</sup> The imbalance in the autonomic nervous activity can contribute to airway narrowing via its effect on the airway smooth muscle, bronchial vessels and mucous glands in the bronchial wall.<sup>1,2</sup> By using the maximum increase in forced expiratory volume in 1.0 s (FEV<sub>1</sub>) following administration of an optimal dose of an anticholinergic agent atropine methionitrate as the index of the amount of cholinergic tone, Gross et al.<sup>3</sup> showed that cholinergic tone in chronic obstructive pulmonary disease (COPD) was increased in proportion to the severity of airway disease. It is therefore likely that abnormal activity of autonomic nerves innervations can contribute to airway narrowing in COPD, and may be relevant to the pathogenesis of COPD. Unfortunately, the actual tone of the airways is difficult to detect non-invasively.

Heart rate variability (HRV) refers to the beat-to-beat alterations in heart rate. It can offer a quantitative assessment of the cardiac autonomic nervous activity and the level of physical fitness.<sup>4</sup> In many basic and clinical studies, the HRV has been used to reflect not only the cardiac autonomic nervous activity, but also the severity of cardiac and non-cardiac diseases.<sup>4-6</sup> The major reason for the interest in measuring HRV stems from its ability to predict survival after heart attack and the prognosis of many major diseases.<sup>4-6</sup>

By using spectral HRV analysis, Volterrani et al.<sup>7</sup> found that COPD patients had abnormal autonomic nervous function, with, in particular, a depressed HRV response to sympathetic and vagal stimuli. They interpreted the increase in the normalized high-frequency power (nHFP) in COPD patients as caused by an increase in vagal activity which could in turn explain in part the reduction in FEV<sub>1</sub> and the increase in bronchoconstriction seen in COPD patients; however, the relation between vagal activity and the severity of airway disease was not shown in their study. In the study of Stein et al.,<sup>8</sup> though significantly positive correlation between FEV<sub>1</sub> and log(HFP) was found in COPD patients, the nHFP and low-/high-frequency power

ratio (LFP/HFP), which were often used as indices of vagal modulation and sympathovagal balance, respectively,<sup>4</sup> were not included.

Stewart et al.<sup>9-11</sup> and Hjalmarssen et al.<sup>12</sup> found that the patients with hypoxemic COPD have a subclinical parasympathetic autonomic neuropathy, with apparent preservation of sympathetic function. Moreover, Stewart et al. found that the autonomic neuropathy correlated significantly with arterial partial pressure of O<sub>2</sub> (PaO<sub>2</sub>) in COPD patients, based on standard autonomic function tests<sup>9</sup> and acetylcholine sweat-spot test.<sup>10</sup> By using spectral HRV analysis, Scalvini et al.<sup>13</sup> found that chronically hypoxemic COPD patients may suffer from abnormal autonomic nervous function and the correction of hypoxemia can partially reverse these abnormalities. It remains to be clarified whether the sympathetic or parasympathetic function of the subjects is correlated with their PaO<sub>2</sub> in COPD patients. Therefore, the aim of this study was to examine the relationship between the derangements in the cardiac autonomic nervous function and the oxygenation status or degree of airflow obstruction in COPD patients by using HRV analysis.

## Methods

### Study subjects

The COPD patients included in this study were clinically stable and ambulatory, and were recruited from the Out-Patient Department of the hospital. COPD was defined according to the criteria of the American Thoracic Society.<sup>14</sup> The aged-matched normal subjects were volunteers recruited from the community. The subjects included in the normal group did not have apparent cardiac, lung or other major diseases that may influence HRV.

### Study protocol

On the day of HRV study, the morning doses of aminophylline,  $\beta_2$ -agonists and steroid were requested to skip, and this status of no medication lasted for about 6 h prior to electrocardiographic

(ECG) recording at 3–4 p.m. so that the drug effects would not be too strong to interfere with the result of HRV analysis or too weak to elicit bronchoconstrictive episode. It may not be ethical to discontinue the medication of the patients for 24 h or longer simply because of study. The Institutional Review Board of the hospital has approved this research. Informed consent was obtained from each patient before study.

### Physiological measurements

All subjects were studied in a quiet air-conditioned room with constant temperature around 25 °C and suitable humidity. After 5 min rest in supine position, a trend of ECG signals was picked up by a bedside ECG monitor (SpaceLab 90621A Monitor, Spacelabs Inc., Redmond, WA) and transmitted to a personal computer for recording. During the recording period, the subjects were asked to close their eyes and relax on the bed. The ECG signals were recorded for 15 min so that at least 512 RR intervals could be obtained for later HRV analysis.

After ECG recording, the forced expiratory volume in the 1.0 s/forced vital capacity ( $FEV_1/FVC$ ) of ordinary pulmonary function test (Spirovit SP-10, Schiller, Switzerland), arterial oxygen saturation from pulse oximetry ( $SpO_2$ ) (BCI 6100 Vital Signs Monitor, Biochem International Inc., Wisconsin) and  $PaO_2$  from arterial blood gases (Automatic Blood Gas System AVL 945, Bedienungs Anleitung, Graz-Austria) were obtained along with other clinical information necessary for the evaluation of the severity of the illness. Arterial puncture was performed on COPD patients only. The  $FEV_1/FVC$  and % predicted of  $FEV_1$  (% $FEV_1$ ) were used as the indices for the evaluation airflow obstruction.  $PaO_2$  was used to represent the oxygenation status of COPD patients, and  $SpO_2$  was used to represent the oxygenation status of normal subjects.

### HRV analysis

The method of HRV analysis was modified from our previous study.<sup>15</sup> In brief, the recorded ECG signals were retrieved to measure the consecutive RR intervals, which are the time intervals between successive pairs of QRS complexes, by using the software for the detection of R waves. The atrial or ventricular arrhythmia was deleted before HRV analysis. If the percentage of deletion was more than 5%, then the data of the patient was excluded from HRV analysis.

The mean, standard deviation ( $SD_{RR}$ ) and coefficient of variation of RR intervals ( $CV_{RR} = SD_{RR}/\text{mean}$

RR interval) in the time domain of 512 RR intervals were calculated by using standard formulae. The power spectrum of these RR intervals was obtained by means of fast Fourier transformation (Mathcad 11, Mathsoft Inc., Cambridge, MA). Zero-frequency component or direct current was excluded before the calculation of the powers. The frequency at which the high-frequency peak occurred (HFF) was used as the breathing frequency of the subject. The area under the spectral peaks within the range of 0.04–0.15, 0.15–0.4, and 0.01–0.4 Hz were defined as the low-frequency power (LFP), HFP, and total power (TP). The normalized HFP ( $nHFP = HFP/TP$ ) was used as the index of vagal activity, the normalized LFP ( $nLFP = LFP/TP$ ) as the index of combined vagal and sympathetic activities, and the LFP/HFP as the index of sympathovagal balance.

### Statistical analysis

Unpaired Student *t*-test or Mann–Whitney rank sum test (SigmaStat 3.0 statistical software, SPSS Inc., Chicago, IL, USA) was employed to compare the normally distributed or distribution-free clinical data and HRV measures between normal subjects and COPD patients. Linear regression analysis was employed to assess the relationships between HRV measures and  $PaO_2$ ,  $SpO_2$ ,  $FEV_1/FVC$ , % $FEV_1$ , or %FVC (% predicted of FVC).

### Results

Thirty clinically stable ambulatory COPD patients and 18 age-matched normal subjects were included in this study. The general and clinical data of normal subjects and COPD patients are shown in Table 1. The  $FEV_1$ ,  $FEV_1/FVC$ , % $FEV_1$ , %FVC, and  $SpO_2$  of COPD patients were all significantly decreased as compared with those of normal subjects.

Table 2 tabulates the HRV measures of normal subjects and COPD patients. The mean,  $SD_{RR}$  and  $CV_{RR}$  in the time domain and the TP, LFP and HFP in the frequency domain were all significantly decreased, whereas the HFF was significantly increased in COPD patients, as compared with normal subjects. In contrast, the  $nHFP$ ,  $nLFP$  and LFP/HFP were not significantly different between normal subjects and COPD patients.

The  $nHFP$  correlated significantly and negatively with  $PaO_2$  (Fig. 1, panel A), and the  $nLFP$  (Fig. 1, panel B) and LFP/HFP (Fig. 1, panel C) correlated significantly and positively with  $PaO_2$  in COPD patients. These spectral HRV measures did not

correlate with the index of airway obstruction FEV<sub>1</sub>/FVC (Fig. 1, panels D–F) in COPD patients. Similarly, no correlation was found between %FEV<sub>1</sub> and spectral HRV measures, including nHFP ( $r = 0.0984$ ,  $P = 0.605$ ), nLFP ( $r = -0.0516$ ,  $P = 0.787$ ), and LFP/HFP ( $r = 0.0095$ ,  $P = 0.96$ ).

## Discussion

Stewart et al.<sup>9–11</sup> and Hjalmarssen et al.<sup>12</sup> have shown that subclinical parasympathetic autonomic neuropathy was a feature of hypoxemic COPD. Since the results of Stewart et al.<sup>9–11</sup> and Hjalmar-

sen et al.<sup>12</sup> were obtained by using the sympathetic and parasympathetic stimulation method of Ewing and Clarke,<sup>16</sup> the autonomic nervous function of the COPD patients at rest was not clear from their studies. By using HRV analysis, Volterrani et al.<sup>7</sup> found that COPD patients had depressed global HRV and increased nHFP at rest. They interpreted the increase in nHFP in COPD patients as caused by an increase in vagal activity that could in turn explain in part the reduction in FEV<sub>1</sub> and the increase in bronchoconstriction seen in COPD patients. In the reports of Stein et al.<sup>8</sup> and Scalvini et al.,<sup>13</sup> some indices of HRV mediated by parasympathetic tone or by both sympathetic and parasympathetic tone in COPD patients were found to be lower than those of the control subjects. In the present study, we found that although global HRV measures were all significantly decreased, the nHFP, nLFP and LFP/HFP of the COPD patients were not significantly different from those of the control subjects. Our observation suggested that both vagal and sympathetic modulations of stable COPD patients at rest were similar to those of normal controls. However, this observation should not be interpreted as no autonomic neuropathy in COPD patients because we did not perform sympathetic and parasympathetic stimulation test in this study. That is, though the resting autonomic nervous activity of the stable COPD patients was similar to that of normal subjects, they might still have abnormal response to sympathetic and parasympathetic stimulation test.

Several reasons might account for the difference between our finding of normal resting autonomic nervous activity and elevated vagal activity in COPD patients in the study of Volterrani et al. Firstly, since the age of the patients in the study of Volterrani et al. was 31–68 years, some of their

**Table 1** General and clinical data of normal subjects and COPD patients.

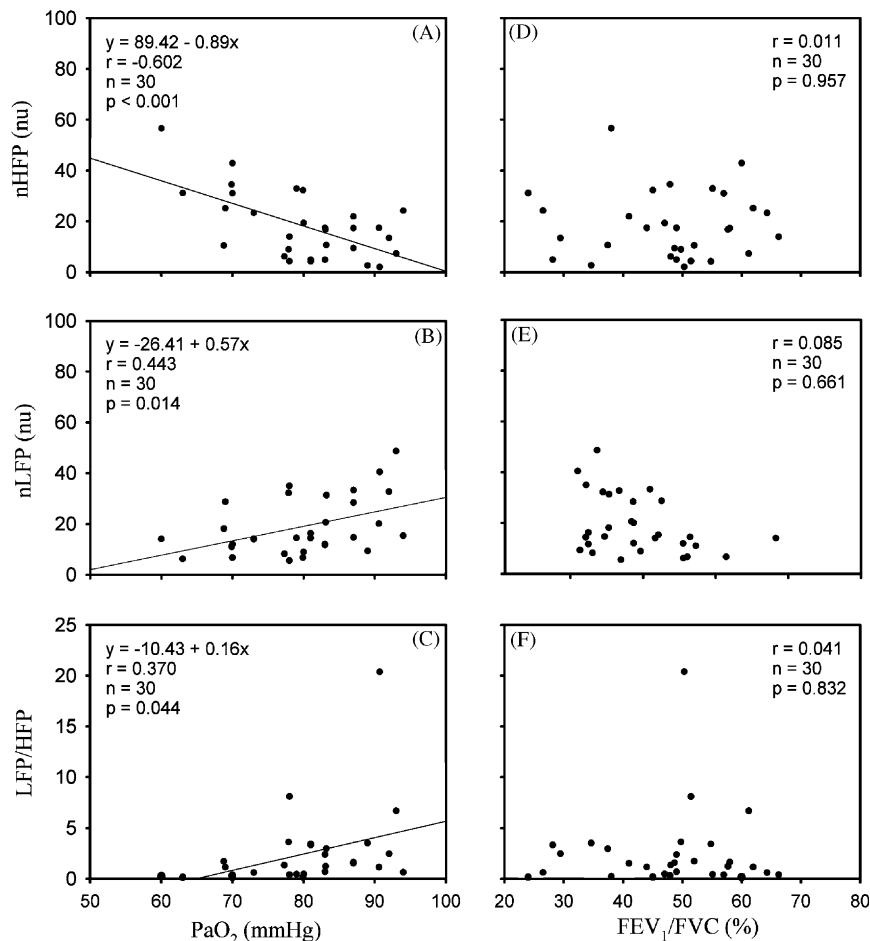
	Normal ( $n = 18$ )	COPD ( $n = 30$ )
Age (years)	64.8 ± 9.0	69.6 ± 6.5
Sex (M/F)	15/3	25/5
Body height (cm)	163.0 ± 6.4	163.5 ± 9.3
Body weight (kg)	63.3 ± 9.1	64.0 ± 13.2
FEV <sub>1</sub> (L)	2.2 ± 0.4	1.3 ± 0.6 <sup>‡</sup>
FEV <sub>1</sub> /FVC (%)	78.3 ± 8.7	50.2 ± 11.0 <sup>‡</sup>
% FEV <sub>1</sub> (% pred)	102.1 ± 14.3	50.5 ± 19.9 <sup>‡</sup>
%FVC (% pred)	106.1 ± 21.9	82.7 ± 20.2 <sup>†</sup>
SpO <sub>2</sub> (%)	96.5 ± 1.2	95.3 ± 2.3 <sup>*</sup>
pH		7.438 ± 0.040
PaO <sub>2</sub> (mmHg)		79.4 ± 11.8
PaCO <sub>2</sub> (mmHg)		38.4 ± 4.5
HCO <sub>3</sub> <sup>-</sup> (mmol/L)		26.9 ± 4.4

Values are mean ± SD. FEV<sub>1,0</sub>, forced expiratory volume in 1.0 s; FVC, forced vital capacity; % FEV<sub>1</sub>, % predicted of FEV<sub>1</sub>; %FVC, % predicted of FVC; SpO<sub>2</sub>, arterial oxygen saturation measured by pulse oximetry; <sup>\*</sup> $P < 0.05$ , <sup>†</sup> $P < 0.01$ , <sup>‡</sup> $P < 0.001$  (unpaired Student *t*-test or Mann-Whitney rank sum test).

**Table 2** Heart rate variability measures in normal subjects and COPD patients.

	Normal ( $n = 18$ )	COPD ( $n = 30$ )
Mn (ms)	917.9 (832.4–1005.0)	694.3 (617.3–738.0) <sup>‡</sup>
SD <sub>RR</sub> (ms)	36.2 (28.0–43.8)	13.8 (10.8–23.1) <sup>‡</sup>
CV <sub>RR</sub> (%)	4.25 (3.10–4.50)	2.20 (1.90–3.10) <sup>‡</sup>
TP (ms <sup>2</sup> )	648.2 (355.6–971.7)	90.1 (39.6–257.5) <sup>‡</sup>
LFP (ms <sup>2</sup> )	114.5 (53.2–176.8)	14.2 (4.7–44.9) <sup>‡</sup>
HFP (ms <sup>2</sup> )	121.9 (38.4–208.3)	13.0 (4.6–30.2) <sup>‡</sup>
HFF (Hz)	0.25 (0.23–0.28)	0.32 (0.26–0.35) <sup>†</sup>
nLFP (nu)	16.9 (12.9–22.6)	14.6 (11.0–28.7)
nHFP (nu)	18.5 (11.0–23.1)	17.0 (7.3–25.1)
LFP/HFP	1.0 (0.7–1.4)	1.3 (0.4–3.0)

Values are median (25–75%). Mn, mean RR interval; SD<sub>RR</sub>, standard deviation of RR interval; CV<sub>RR</sub>, coefficient of variation of RR interval; TP, total power; LFP, low-frequency power; HFP, high-frequency power; HFF, frequency of high-frequency peak; nLFP, normalized low-frequency power; nHFP, normalized high-frequency power; LFP/HFP, low-/high-frequency power ratio. <sup>†</sup> $P < 0.01$ , <sup>‡</sup> $P < 0.001$  (Mann-Whitney rank sum test).



**Figure 1** The normalized high-frequency power (nHFP) correlated significantly and negatively with  $\text{PaO}_2$  (panel A), and the normalized low-frequency power (nLFP) (panel B) and low-/high-frequency power ratio (LFP/HFP) (panel C) correlated significantly and positively with the  $\text{PaO}_2$  in COPD patients. There was no correlation between  $\text{FEV}_1/\text{FVC}$  and nHFP (panel D), nLFP (panel E) or LFP/HFP (panel F).

young patients might be asthmatic patients rather than COPD, and asthmatics were already known to have vagal overactivity.<sup>17</sup> Secondly, the study of Volterrani et al. was performed in the morning after discontinuing the treatment with aminophylline, oral  $\beta_2$ -agonist and steroid medications for 24h, whereas we performed the study in the afternoon and the medical treatment was discontinued for less than 24h. The discontinuation of medical treatment for 24h might cause rebound vagal overactivity in those patients who had been using aminophylline, oral  $\beta_2$ -agonist and steroid medications as maintenance therapy for a long period of time. Thirdly, the frequency range for the HFP was 0.18–0.35 Hz in the study of Volterrani et al., whereas the frequency range for the HFP in this study was 0.15–0.4 Hz. Different frequency range might lead to different values for the HFP and nHFP.

Similar to the studies of Stein et al.<sup>8</sup> and Scalfini et al.,<sup>13</sup> we found that there were significant differences in TP, LFP, and HFP between COPD

patients and control subjects. However, we found that the nHFP, nLFP, and LFP/HFP of COPD patients were not significantly different from those of the control subjects. The representation of LFP and HFP in normalized units emphasizes the controlled and balanced behavior of the two branches of the autonomic nervous system, while the normalization procedure tends to minimize the effect of the changes in TP on the values of LFP and HFP components.<sup>4</sup> Though there was a significant difference in LFP and HFP between COPD patients and control subjects, this result may not be interpreted as significant autonomic dysfunction in resting stable COPD patients because no significant difference in nLFP and nHFP was found between these two groups of subjects.

Stewart et al.<sup>9</sup> found that the degree of parasympathetic autonomic dysfunction correlated significantly with  $\text{PaO}_2$  whilst the sympathetic function was relatively normal in COPD patients. By measuring the pancreatic polypeptide, Hjalmsen



et al.<sup>12</sup> also found that the basal concentration of pancreatic polypeptide was increased and had a significant negative correlation with FEV<sub>1</sub>, SaO<sub>2</sub> and PaO<sub>2</sub> in COPD patients. These studies suggested that the vagal activity of COPD patients was related to the oxygenation status of the patients. Similarly, we found that the index of vagal activity of COPD patients correlated significantly and negatively with PaO<sub>2</sub>, and the index of sympathetic activity correlated significantly and positively with PaO<sub>2</sub>. However, both indices of autonomic nervous activity and PaO<sub>2</sub> did not correlate with either FEV<sub>1</sub>/FVC or %FEV<sub>1</sub> in COPD patients.

The high metabolic activity of nerves makes them extremely susceptible to hypoxemia and could cause a reversible impairment in electrophysiological function.<sup>9</sup> Since the SpO<sub>2</sub> of our COPD patients was significantly lower than that of normal control (Table 1), it seemed possible that chronic, mild hypoxemia might cause hypoxic damage to the nerve which in turn could lead to increased cardiac vagal activity and decreased sympathetic activity in stable but chronically hypoxemic COPD patients.<sup>9–12</sup>

One might speculate that the negative correlation between nHFP and PaO<sub>2</sub> in COPD patients could be caused by respiration-related mechanism, because hypoxemia can lead to hyperventilation and because the amplitude of the high-frequency component can be significantly affected by respiratory frequency and tidal volume independent of the level of cardiac vagal outflow.<sup>18–21</sup> Since no correlation was found between PaCO<sub>2</sub> and nHFP in this study, it was unlikely that the correlation between nHFP and PaO<sub>2</sub> was caused by respiration-related mechanism in COPD patients.

The cholinergic tone in COPD patients was shown to be increased in proportion to the severity of airway disease.<sup>3</sup> In addition, significant correlations were found between FEV<sub>1</sub>/FVC and some indices of HRV (natural log of LFP and HFP) in the study of Stein and associates.<sup>8</sup> However, we found that FEV<sub>1</sub>/FVC and %FEV<sub>1</sub> did not correlate significantly with the indices of autonomic nervous function (nLFP, nHFP and LFP/HFP) in COPD patients. The representation of LFP and HFP in normalized units might account for the difference between the results of the present study and the study of Stein et al. The reason for no significant correlation between HRV measures and FEV<sub>1</sub>/FVC or %FEV<sub>1</sub> in this study might be that HRV might not reflect the actual tone of the airway in COPD patients.

The HRV can be influenced by the circadian rhythm,<sup>22</sup> the medication, and the respiration rate of the patients. To minimize the potential impact of circadian rhythm HRV, the ECG signals of all

subjects were picked up at 3–4 p.m. in this study. The insufficient duration of discontinuation of sympathomimetic medication taken by the patients might have some effect on their HRV. However, the sympathomimetic agents of the patients might not be a problem because: (1) The duration of discontinuation of sympathomimetic agents was in fact longer than 12 h; (2) The increase in heart rate and respiratory rate in our patients might be caused by not only sympathomimetic agents, but also the disease itself, such as airway obstruction and hypoxemia; (3) The effect of heart rate on the time domain HRV measures can be minimized by using CV<sub>RR</sub> which is the SD<sub>RR</sub> divided by mean RRI, and the effect of heart rate on frequency domain HRV measures can be minimized by excluding the zero-frequency component or direct current or mean RRI before the calculation of the powers by using Fast Fourier Transform.

Though there was a significant difference in HFF ( $0.26 \pm 0.04$  vs.  $0.30 \pm 0.06$  Hz [mean  $\pm$  sd],  $P < 0.01$ ) between normal subjects and COPD patients, we did not try to control and adjust the respiratory rate of the patients to that of normal subjects because such maneuver would inevitably interfere with the autonomic nervous system of the patients, leading to unreal and biased HRV. If the patients had slight tachypnea because of airway obstruction and hypoxemia, it would be more natural to record and analyze the rhythm of their heart beating as they really were. This was the reason why we made no attempt to control the respiratory rate of the COPD patients in this study.

In conclusion, the resting autonomic nervous function of COPD patients is not significantly different from that of normal subjects. The degree of airway narrowing is not directly related to the cardiac autonomic nervous function; however, chronic hypoxemia can increase the cardiac vagal activity and depress the sympathetic activity of COPD patients. The worse the oxygenation status of the patients is, the more cardiac vagal and lesser cardiac sympathetic activities the patients have.

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